氏　　名	MONIRUZZAMAN
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審査委員	主査　教授　尾関　祐二
	副査　教授　清水　猛史
	副査　教授　小島　秀人

別紙様式３（課程博士・論文博士共用）

論 文 内 容 要 旨

※整理番号	911	(ふりがな) 氏　　名	(モニルザマン) MONIRUZZAMAN
学位論文題目	Relationship Between Step Counts and Cerebral Small Vessel Disease in Japanese Men （日本人男性における歩数と脳小血管病との関連）		

BACKGROUND AND PURPOSE: Cerebral small vessel disease (CSVD) is a common feature of the aging brain and neurological disease in adults and the elderly. It causes stroke, cognitive decline, depression, dementia, including Alzheimer's disease, and death; however, there are no specific preventive or therapeutic measures to ameliorate this condition. Steps per day may contribute to its prevention. The primary aim of the present study was to investigate the association between step counts at baseline and MRI CSVD features measured by white matter hyperintensities (WMHs), lacunar infarcts (LIs), and cerebral microbleeds (CMBs) in a follow-up 5 years later in general Japanese man. The relationship between step counts and WMH volumes (WMHVs) was also examined.

METHODS: We analyzed data from 680 men who were free of stroke and participated in the SESSA (Shiga Epidemiological Study of Subclinical Atherosclerosis)—a population-based observational study. Seven-day step counts were assessed at baseline (2006–2008) using a pedometer. CSVD was assessed at follow-ups (2012–2015) based on deep and subcortical white matter hyperintensities (DSWMHs), periventricular hyperintensities (PVHs), LIs, and CMBs on brain MRI. Two neurosurgeons, certified by the Japan Neurosurgery Society, independently assessed all MRI images in duplicate. Using a logistic regression analysis, we computed the adjusted odds ratios (ORs), with 95% CIs, of prevalent CSVD according to quartiles of step counts (reference: Q1). We mainly ran 2 models in these analyses: model 1 was adjusted for age (years) and model 2 for age and smoking and drinking status (current, past, and never). We also ran another model: model 3 was adjusted for variables in model 2 plus diabetes, dyslipidemia, and hypertension (yes/no) to explore what their presence may explain additional associations.

（備考）１．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字
程度でタイプ等を用いて印字すること。
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We also investigated the association between step counts and WMHVs (total WMHVs, deep and subcortical WMHVs, and periventricular hyperintensity volumes) using a quantile regression. We computed β-coefficients and the corresponding 95% CI for each WMHV per 1000 increments in a 7-day average step counts at the 25th, 50th, and 75th percentiles. We reproduced the same models of the logistic regression, with the addition of the total intracranial volume to the models. We declared P less than the 2-sided significance level of 0.05 to be significant for all analyses. All analyses were performed using SAS version 9.4.

RESULTS: The mean (SD) age and educational attainment of all participants were 63.6 (9.2) and 12.7 (2.9) years, respectively. The 7-day average step count was 8525 (3537). Steps per day were significantly associated with lower ORs, with the lowest at Q3 (8175–10 614 steps/day), of higher (versus low or no burden) DSWMHs (OR, 0.52 [95% CI, 0.30–0.89]), PVHs (0.50 [95% CI, 0.29–0.86]), and LIs (0.52 [95% CI, 0.30–0.91]) compared with Q1 (≤6060 steps/day) but not CMBs. An inverse linear association was observed between step counts and WMHVs. These associations were independent of age and smoking and drinking status and remained consistent when adjusted for vascular risk factors.

DISCUSSION: In this population-based study on Japanese men who were free from stroke and cognitive decline, physical activity assessed by the 7-day average step counts was significantly associated with reduced MRI CSVD features (DSWMHs, PVHs, and LIs), except for CMBs, demonstrating a J-shaped relationship. We also found inverse linear associations between step counts and WMHVs (total WMHVs, DSWMHVs, and PVHs). These associations were independent of age and smoking and drinking status. These relationships remained consistent and similar in other models adjusted for vascular risk factors. To the best of our knowledge, this is the first study to investigate the associations between step counts and MRI CSVD features measured by WMHs (visual ratings and volumetric measures), LIs, and CMBs.

CONCLUSIONS: Our study showed a J-shaped relationship between physical activity assessed by step counts and prevalent subclinical CSVD (DSWMHs, PVHs, and LIs) in healthy Japanese men, with the significantly lowest risk being observed among participants who had ≈8000 to 10 000 steps/day, thereby supporting the Japanese and global public health recommendations. We also found that higher step counts significantly related to lower WMH volumes.

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学位論文審査の結果の要旨

整理番号	911	氏　名	MONIRUZZAMAN
論文審査委員			

（学位論文審査の結果の要旨）

本論文では一般日本人男性680人を対象に、１日の歩数（日常生活上の７日間連続測定したその平均値）と５年間に生じた脳小血管病（大脳深部・皮質下白質病変、脳室周囲病変、ラクナ梗塞、微小脳出血）との関係をロジスティック回帰分析で評価した。評価では3種類のモデルを用いた（モデル１：年齢で補正、モデル２：補正に喫煙、飲酒を追加、モデル３：モデル２に糖尿病、脂質代謝異常、高血圧を追加）。歩数の少ない順に対象者を人数が均等になるように４群に分けて、最も歩数が少ない群を基準としてオッズ比を比較した。また大脳深部・皮質下白質病変または脳室周囲病変及び両方を合わせた体積と歩数の関係を分位点回帰法で評価した。

以上より以下の結果を得た。

1) 最も歩数が少ない群よりも多い群のほうが微小脳出血を除いたいずれの指標でもオッズ比が低く、２番目に歩数が多い群が最もオッズ比が低かった。
2) 分位点回帰では25%、50%、75%のいずれの分位でも、すべての因子が歩数と有意な負の相関を示し、歩数が多いほど病変の体積が小さかった。

以上より、歩数と脳小血管病の間にはＪ型の関係があり大脳深部・皮質下白質病変と脳室周囲病変の体積は歩数が多いほど小さくなることが明らかになり、歩行の中枢神経保護作用が示された。また最終試験として論文内容に関した試問を施行し合格と判断されたため、博士（医学）の学位論文に値するものと認められた。

（総字数　597字）

（令和　３年　１月　25日）